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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,840	01/31/2001	Brian P. Dwyer	257/245	2714
9629	7590	11/28/2006	EXAMINER	
MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004			TRAN, MY CHAU T	
			ART UNIT	PAPER NUMBER
			1639	
DATE MAILED: 11/28/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/775,840

Applicant(s)

DWYER ET AL.

Examiner

MY-CHAU T. TRAN

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 41,44,49-52,54-57,59,62,64-66,71 and 114-119 is/are pending in the application.
- 4a) Of the above claim(s) 116 and 118 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 41,44,49-52,54-57,59,62,64-66,71,115,117 and 119 is/are rejected.
- 7) ☒ Claim(s) 114 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 January 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

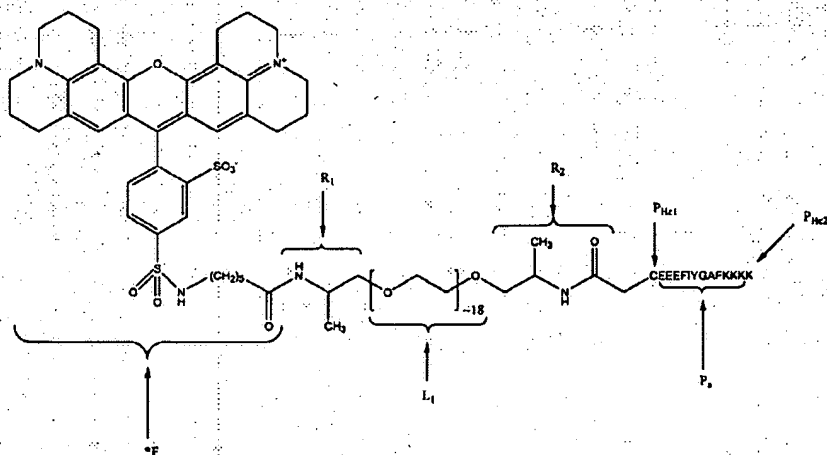
DETAILED ACTION***Application and Claims Status***

1. Applicant's amendment and response filed 08/04/2006 are acknowledged and entered.
2. Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, and 114-119 were pending. Applicants have amended claims 41, 57, and 119. No claims were added and/or cancelled. Therefore, claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, and 114-119 are currently pending.

Election/Restrictions

3. The instant species election requirement is still in effect as there is no allowable generic or linking claim. Applicant has elected **without** traverse the following species for the elected invention (Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, and 114-119) in the reply filed on 03/12/2004:

For the single specific species of a water-soluble pegylated kinase substrate that would read on the formula of $*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)_y$, applicant elected the



compound:

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Note: the elected species is disclosed in the specification of page 34 (scheme 2), which is Texas Red-Jeffamine₉₀₀-CEEEFIYGAFKKKK [SEQ. ID. NO.: 1]. Furthermore, it is noted that “For the portion (R₃-L₂-R₄-T)_y, y = 0; therefore (R₃-L₂-R₄-T) is removed” (see Exhibit A of the response filed 03/12/2004). P_{Hc1} is C (cysteine); therefore in the formula of P_{Hc1} = A_c(A_H)_nA_m, A_c = cysteine, A_m = covalent bond, and since n = 0 A_H is 0. P_{Hc2} is K (lysine); therefore in the formula of P_{Hc2} = A_m(A_H)_nA_c, A_c = carboxylic acid moieties since y = 0, A_m = covalent bond, and since n = 0, A_H is 0. P_s is EEEFIYGAFKKK (SEQ. ID. No. 1). Jeffamine₉₀₀ is a polyethylene glycol with the molecular weight of 900.

4. Claims 116 and 118 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to *a nonelected species*, i.e. the elected species of L₁ is polyethylene glycol with the molecular weight of 900 and L₂ is ‘removed’, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 03/12/2004.

5. Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, 114, 115, 117, and 119 are under consideration in this Office Action.

Status of Claim(s) Objection(s) and /or Rejection(s)

6. The rejections of claims 41, 44, 49-51, 54-57, 71, 115, 117, and 119 under 35 USC 102(b) as being anticipated by Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472) alone or as evidenced by Shimizu et al. (US Patent 4,640,835) regarding the newly added limitation that polyethylene glycol (PEG) having ‘*the molecular weight of less than*

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about 2000 Daltons' have been withdrawn in light of applicant's amendments of claims 41 and 119, and arguments.

7. The rejection of claims 41, 44, 49-52, 54-57, 59, 62, 64-66, and 71 under 35 USC 103(a) as being obvious over Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472), Shimizu et al. (US Patent 4,640,835), and Pomroy et al. (*Biochemical and Biophysical Research Communications*, 1998, 245(2): 618-621) has been withdrawn in view of applicant's amendments of claims 41 and 119, and arguments.

New Rejection(s) – Necessitated by Amendment

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 41, 44, 49-52, 54-57, 59, 62, 64-66, 71, 115, 117, and 119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A. Both the amended claims 41 and 119 recite the limitation of "*molecular weight of less than 2000 Daltons*" regarding the instantly claimed compound represented by the variable of "*L₁*" and "*L₂* (Note: this variable is drawn to *a nonelected species*; see paragraph 3 above)".

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This limitation, which extends the '*molecular weight*' range (i.e. the upper limit is 2,000, which does not include 2,000, and no lower limit) of the instantly claimed compound, is not supported by the originally filed specification and/or claims; nor has applicant provided any indication where such support exists. See 37 CFR 1.121 (b)(2)(iii), and the MPEP § 714.02, 3rd paragraph, last sentence; MPEP § 2163.02; and MPEP § 2163.06. For example, the instant specification discloses various ranges for the hydrophilic polymers, i.e. "*Various lengths of hydrophilic polymers may be employed, ranging in size from about 80 Daltons (two ethylene glycol units) to about 4000 Daltons, more preferably from about 100 to about 2000 Daltons, more preferably from about 500 to about 1500 Daltons, and most preferably from about 800 to about 1000 Daltons. Polyethylene glycol polymers ranging in size from about 230 to about 2000 Daltons are particularly preferred for use in the invention*" (see specification, pg. 16, lines 3-8).

Consequently, the limitation of "*molecular weight of less than 2000 Daltons*" has no specification or original claim support, and it is considered new matter. If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the originally filed specification and/or claims.

B. The amended claim 57 recites the limitation of "*a molecular weight from about 230 to less than 2000 Daltons*" regarding the instantly claimed polyethylene glycol regarding the instantly claimed compound represented by the variable of " L_1 " and " L_2 (Note: this variable is drawn to *a nonelected species*; see paragraph 3 above)". This limitation, which restricts the '*molecular weight*' range (i.e. the upper limit is 2,000, which does not include 2,000, and the lower limit is 230, which may include 230) of the instantly claimed polyethylene glycol, is not supported by the originally filed specification and/or claims; nor has applicant provided any

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indication where such support exists. See 37 CFR 1.121 (b)(2)(iii), and the MPEP § 714.02, 3rd paragraph, last sentence; MPEP § 2163.02; and MPEP § 2163.06. For example, the instant specification discloses various ranges for polyethylene glycol, i.e. *"Various lengths of hydrophilic polymers may be employed, ranging in size from about 80 Daltons (two ethylene glycol units) to about 4000 Daltons.... Polyethylene glycol polymers ranging in size from about 230 to about 2000 Daltons are particularly preferred for use in the invention"* (see specification, pg. 16, lines 3-8). Consequently, the limitation of *"a molecular weight from about 230 to less than 2000 Daltons"* has no specification or original claim support, and it is considered new matter. If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the originally filed specification and/or claims.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

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invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 41, 44, 49-52, 54-57, 71, 115, 117, and 119 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472) in view of Liu et al. (WO 00/12,458; *Published 03/09/2000*).

For *claims 41, 44, 49-52, 71, 115, 117, and 119*, Belcheva et al. disclose the water-soluble fluorescein polymer-peptide conjugates (see e.g. pg. 471, left col., lines 12-25, and 35-39; pg. 472, lines 2-6; pg. 471, fig. 1; pg. 472, fig. 2; pg. 472, Table 1). The peptide (P_s) is 5 amino acids in length (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). The polymer is polyethylene glycol (PEG) (refers to instant claimed L_1 is polyethylene glycol) with a MW of either 2,000 or 5,000 (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6). The water-soluble fluorescein polymer-peptide conjugates of Belcheva et al., i.e. GRGDY-PEG-fluorescein, read on the claimed substrate member with the general formula of $*F-R_1-L_1-R_2-P_{Hc1}-P_S-P_{Hc2}-(R_3-L_2-R_4-T)_y$, wherein y is 0, $*F$ is fluorescein (refers to instant claims 49-51), L_1 is polyethylene glycol (PEG), R_1 and R_2 are a covalent bond, P_{Hc1} is a covalent bond, i.e. in the formula of $P_{Hc1} = A_c(A_H)_nA_m$: A_c and A_m = covalent bond, and since $n = 0$, A_H is 0, and P_{Hc2} is a covalent bond with a carboxylic acid moiety, i.e. in the formula of $P_{Hc2} = A_m(A_H)_nA_c$: A_c = carboxylic acid moieties since $y = 0$, A_m = covalent bond, and since $n = 0$, A_H is 0 (see e.g. pg. 471, left col., lines 17-18, and 35-39; pg. 472, lines 2-6).

The teachings of Belcheva et al. differs from the presently claimed invention as follows:

For *claims 41, 54-57, and 119*, Belcheva et al. fail to disclose the polymer, i.e. PEG, in the range of less than 2000.

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However, Liu et al. teach the limitations that are deficient in Belcheva et al.

For *claims 41, 54-57, and 119*, Liu et al. disclose PEG-peptide conjugates (see e.g. pg. 1, lines 10-14; pg. 2, lines 15-24; pg. 9, lines 20-25). Liu et al. teach lower molecular weight PEG, wherein the molecular weight PEG ranges from 200-2,000 (see e.g. pg. 7, lines 8-31; pg. 9, line 31 thru pg. 10, line 29). Moreover, Liu et al. disclose that lower molecular weight PEG, i.e. ranges from 200-2,000, does not create steric hindrances that interfere with receptor or substrate binding (see e.g. pg. 2, lines 17-20).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to include lower molecular weight PEG, i.e. less than 2000, as taught by Liu et al. in the conjugates of Belcheva et al. One of ordinary skill in the art would have been motivated to include lower molecular weight PEG, i.e. less than 2000 in the conjugates of Belcheva et al. for the advantage of providing PEG polymer that does not create steric hindrances that interfere with receptor or substrate binding (Liu: pg. 2, lines 17-20). Moreover in both conjugates of Belcheva et al. and Liu et al., the prerequisite structural feature of the conjugate is the PEG, i.e. analogous art, (Belcheva: pg. 471, left col., lines 17-18, and 35-39; Liu: pg. 1, lines 10-14). Furthermore, one of ordinary skill in the art would have a reasonable expectation of success in the combination of Belcheva et al. and Liu et al. because the type of molecular weight PEG use would be a choice of experimental design and is considered within the purview of the cited prior art.

Therefore, the combine teachings of Belcheva et al. and Liu et al. do render the product of the instant claims *prima facie* obvious.

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13. Claims 59, 62, and 64-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Belcheva et al. (*Polymeric Materials Science and Engineering*, 1998, 79:471-472) in view of Liu et al. (WO 00/12,458; *Published 03/09/2000*) as applied to claims 41, 44, 49-52, 54-57, 71, 115, 117, and 119 above, and further in view of Pomroy et al. (*Biochemical and Biophysical Research Communications*, 1998, 245(2): 618-621).

For **claims 41, 44, 49-52, 54-57, 71, 115, 117, and 119**, the combine teachings of Belcheva et al. and Liu et al. teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 41, 44, 49-52, 54-57, 71, 115, 117, and 119.

The combine teachings of Belcheva et al. and Liu et al. differs from the presently claimed invention as follows:

For **claim 59**, the combine teachings of Belcheva et al. and Liu et al. fail to include that R_2 is a thioether linkage.

For **claim 62**, the combine teachings of Belcheva et al. and Liu et al. fail to teach that for at least one P_{Hc1} and P_{Hc2} , the A_c is a cysteine.

For **claims 64-66**, the combine teachings of Belcheva et al. and Liu et al. fail to disclose that the "end" residues (P_{Hc1} and P_{Hc2}) of the peptide has a different net charged.

However, Pomroy et al. teach the limitations that are deficient in the combine teachings of Belcheva et al. and Liu et al.

For **claims 59 and 62**, Pomroy et al. disclose hydrophobic peptides wherein the peptide is coupled to the polyethylene glycol (PEG) by way of the cysteine with a PEG-a-cys reagent (Abstract; pg. 619, left col., line 60 to right col., line 2; fig. 2) (refers to claims 41, 44, and 59).

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Pomroy et al. disclose that there are several advantages for attaching Cys side chain to a thiol-reactive PEGs: 1) it can perform under mild reaction conditions allowing for the PEGylation of a target protein under non-denaturing conditions; 2) it is highly targeted; and the disulfide bond between the thiol-reactive Peg and the protein is cleavable with suitable disulfide-reducing agents (pg. 619, right col., lines 29-40).

For *claims 64-66*, the peptide of Pomroy et al. comprises "end" residues (P_{Hc1} and P_{Hc2}) with different net charged (pg. 619, right col., lines 53-55) (refers to claims 64-66).

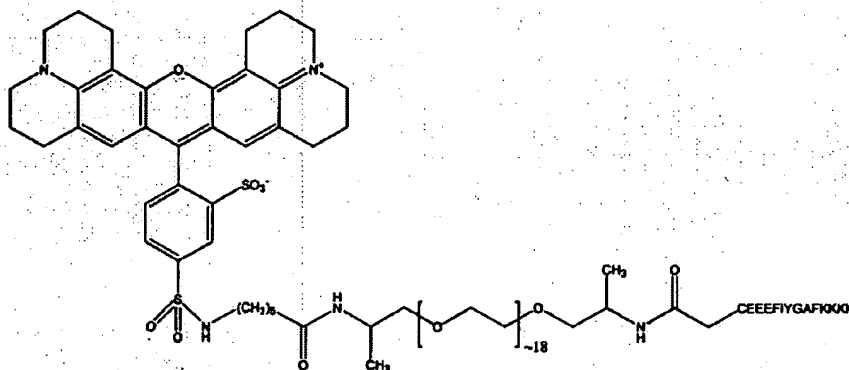
It would have been obvious to a person of ordinary skill in the art at the time the invention was made to disclose attaching the PEG to peptide via the cysteine (i.e. R_2 is a thioether linkage and A_c is a cysteine) and the "end" residues (P_{Hc1} and P_{Hc2}) of the peptide having a different net charged as taught by Pomroy et al. in the conjugates of Belcheva et al. and Liu et al. One of ordinary skill in the art would have been motivated to disclose attaching the PEG to peptide via the cysteine (i.e. R_2 is a thioether linkage and A_c is a cysteine) and the "end" residues (P_{Hc1} and P_{Hc2}) of the peptide having a different net charged in the conjugates of Belcheva et al. and Liu et al. for the advantage of providing a cleavable disulfide bond between the thiol-reactive PEG and the protein (Pomroy: pg. 619, right col., lines 37-40). Moreover, both Belcheva et al. and Pomroy et al. disclose composition wherein the peptide is coupled to the polyethylene glycol, i.e. analogous art, (Belcheva: pg. 471, left col., lines 12-25, and 35-39; Pomroy: pg. 618, right col., lines 18-33). Furthermore, one of ordinary skill in the art would have a reasonable expectation of success in the combination of Belcheva et al., Liu et al., and Pomroy et al. because Pomroy et al. disclose the success of PEGylation of the peptide using PEG-a-Cys reagent (pg. 620, lines 5-32; fig. 2).

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Therefore, the combine teachings of Belcheva et al., Liu et al., and Pomroy et al. do render the product of the instant claims *prima facie* obvious.

Allowable Subject Matter

14. Claim 114 is allowable. The following is a statement of reasons for the indication of allowable subject matter: The cited prior art does not teach or fairly suggest the water-soluble peptidic substrate of claim 114 with the formula of



Conclusion

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 571-272-0810. The examiner can normally be reached on Monday: 8:00-2:30; Tuesday-Thursday: 7:30-5:00; Friday: 8:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

mct
November 16, 2006


JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER